

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference PC507PR	FOR FURTHER ACTION	See item 4 below
International application No. PCT/IB2004/002208	International filing date (<i>day/month/year</i>) 21 June 2004 (21.06.2004)	Priority date (<i>day/month/year</i>) 23 June 2003 (23.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ROTTAPHARM S.P.A.		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> .1(a).																								
2.	This REPORT consists of a total of 8 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input checked="" type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 03 January 2006 (03.01.2006)
Facsimile No. +41 22 740 14 35	Authorized officer <div style="text-align: center; font-weight: bold;">Idhir Britel</div>
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 09 DEC 2004

WIPO PCT

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To:

see form PCT/ISA/220

29/12

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/B2004/002208

International filing date (day/month/year)
21.06.2004

Priority date (day/month/year)
23.06.2003

International Patent Classification (IPC) or both national classification and IPC
C07C231/24, C07C233/12

Applicant
ROTTA RESEARCH LABORATORIUM S.P.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1b/s(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Authorized Officer

Lorenzo Varela, M.J.

Telephone No. +49 89 2399-8239



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/B2004/002208

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002208

Box No. II Priority

1. ☒ The following document has not been furnished:

☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-5
	No: Claims	6-14
Inventive step (IS)	Yes: Claims	
	No: Claims	1-5
Industrial applicability (IA)	Yes: Claims	1-14
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

- D1: US-A-5 602 179 (MAKOVEC FRANCESCO ET AL) 11 February 1997 (1997-02-11)
- D2: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KATSCHINSKI, MARTIN: "Loxiglumide. Rotta Research" XP002306781 retrieved from STN Database accession no. 2002:580170
- D3: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VARGA, GABOR: "Dexloxiglumide (Rotta Research Lab)" XP002306782 retrieved from STN Database accession no. 2002:580010
- D4: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FRIED, M. ET AL: "The role of fat and cholecystokinin in functional dyspepsia" XP002306783 retrieved from STN Database accession no. 2002:577063
- D5: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; PERSIANI, S. ET AL: "Pharmacokinetics of dexloxiglumide after administration of single and repeat oral escalating doses in healthy young males" XP002306784 retrieved from STN Database accession no. 2002:485631
- D6: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MASELLI, M. A. ET AL: "Effect of three nonpeptide cholecystokinin antagonists on human isolated gallbladder" XP002306785 retrieved from STN Database accession no. 2002:50662
- D7: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; REVEL, LAURA ET AL: "Dexloxiglumide: CCK1 (CCKA) receptor antagonist treatment of irritable bowel syndrome" XP002306939 retrieved from STN Database accession no. 1999:656782
- D8: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; VARGA, GABOR ET AL: "Different actions of CCK on pancreatic and gastric growth in the rat: effect of CCKA receptor blockade" XP002306940 retrieved from STN Database accession no. 1998:370098
- D9: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SCARPIGNATO, C. ET AL: "Effect of dexloxiglumide and spiroglumide, two new CCK-receptor antagonists, on gastric emptying and secretion in the rat: Evaluation of their receptor selectivity in vivo" XP002306786

retrieved from STN Database accession no. 1996:398396

1. The present application relates to a method for the production of crystalline dexloxiglumide by crystallization of the crude product from isopropyl ether as a solvent. Dexloxiglumide in crystalline form and pharmaceutical compositions comprising dexloxiglumide for the treatment of diseases of the digestive tract are claimed as well.
2. D1 discloses a method for the preparation of crystalline dexloxiglumide by crystallization of the crude product from a mixture water/alcohol as a solvent; dexloxiglumide in crystalline form and pharmaceutical compositions comprising dexloxiglumide for the treatment of diseases of the digestive tract are also disclosed.
3. D2-D9 disclose dexloxiglumide and pharmaceutical compositions comprising dexloxiglumide for the treatment of diseases of the digestive tract.

Novelty

4. The subject-matter of claims 6-14 is not novel in the sense of Art. 33(2) PCT. A product is not novel because it has been prepared by a new method: in the present case the crystallization of dexloxiglumide with a different solvent from the one used in the prior art. Furthermore, pharmaceutical compositions comprising dexloxiglumide for the treatment of diseases of the digestive tract are known as well. Hence, the subject-matter of the present claims 6-14 is anticipated by the prior art D1-D9 (see paragraphs 2 and 3 above).
5. The subject-matter of claims 1-5 is novel in the sense of Art. 33(2) PCT. None of the available documents of the prior art discloses a method for the production of crystalline dexloxiglumide by crystallization of the crude product from isopropyl ether as a solvent (see paragraph 2 above).

Inventive step

6. The subject-matter of claims 1-5 cannot be considered to involve an inventive step in the sense of Art. 33(3) PCT.
- 6.1. The closest state of the art, D1, discloses a method for the preparation of crystalline

dexloxiglumide by crystallization of the crude product from a mixture water/alcohol as a solvent; the crystallization of related compounds using isopropyl ether is disclosed as well (see the tables in D1).

- 6.2. The problem to be solved in the application can be seen in the provision of an improved/alternative process for the preparation of crystalline dexloxiglumide.
- 6.3. In view of D1, it would be obvious for the skilled person in the art the crystallization of dexloxiglumide using the solvent disclosed in D1 for related products to crystallize dexloxiglumide in order to provide an alternative/improved method. Furthermore, the crystallization of a known product is normal practice for the skilled person in the art. Hence, an inventive step cannot be acknowledged.

Further comments

7. The conditions under which crystallisation is carried out are very important in order to obtain a specific type of crystal. Since independent claim 1 does not contain these features (the specific conditions for the crystallization: the ratio product/solvent, the temperature/ratio and period of seeding and cooling), it does not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.
8. Features introduced by terms like "preferably" or "particularly" have no limiting effect on the scope of the claim including them (see PCT Guidelines, C-III, 4.6). The presence of such non-limiting features is however detrimental to the conciseness of claims 5 and 14, contrary to Art. 6 PCT.
9. The use of the word "about", especially in connection with numerical ranges, is generally regarded as rendering the determination of the exact scope of the range difficult. When used in a claim as well as in the description, this results in lack of clarity, contrary to Art. 6 PCT. Therefore, the description needs to be adequately redrafted by deletion of said word in each of its occurrences.
10. The last paragraph in the description should have been included in claims 3, 6-8 in order to meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any claim must contain all the technical features essential to the

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/002208

definition of the invention.

11. There is a mistake when disclosing the CAS registry number of dexloxiglumide; the right number is 119817-90-2.
12. Figures 1B and 2B should have been named comparative examples.
13. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D2-D9 is not mentioned in the description, nor are these documents identified therein.
14. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims.
15. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 19(2) and 34(2) PCT, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.